Factors Influencing Age and Strain-Related Susceptibility to 3-Methylcholanthrene Carcinogenicity

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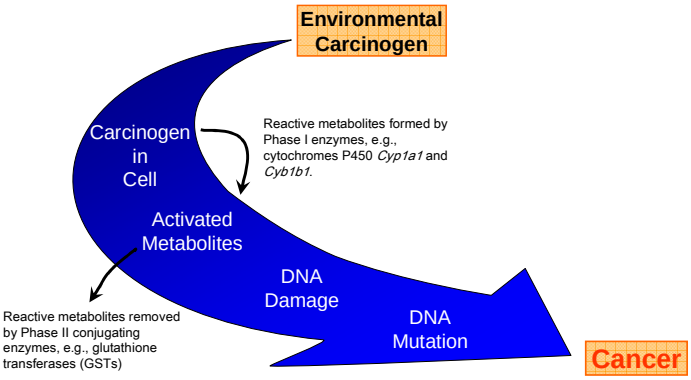
Background

Fetal mice are more susceptible than adults to some chemical carcinogens. The BALB/c (BC) strain of mice is more susceptible to chemical carcinogenesis, while the C57BL/6 (B6) strain is less susceptible than other strains. Polycyclic aromatic hydrocarbons (PAHs) are chemicals formed during combustion processes, many of which are carcinogenic. PAHs are believed to initiate cancer by being metabolized to highly reactive forms by cellular enzymes known as Phase I enzymes. The reactive metabolites may be removed from the cell by enzymes known as Phase II enzymes. Metabolites not removed by Phase II enzymes may bind to cellular macromolecules, including DNA. The resultant DNA damage, if not accurately removed by repair enzymes, may lead to the formation of mutations. Mutations in critical oncogenes represent key molecular events in carcinogenesis by PAHs.



Questions

- Are differences in carcinogen susceptibility between strains of mice due to differences in metabolic activation and DNA binding?
- Are differences in carcinogen susceptibility between fetal and adult mice due to differences in metabolic activation and DNA binding?

Approach

- Mice were exposed *in utero* to 3-methylcholanthrene (3MC), a carcinogenic polycyclic aromatic hydrocarbon, by injecting the mothers ip on the 17th day of gestation.
- BC strain (sensitive to 3MC carcinogenesis) and B6 strain (resistant to carcinogenesis) mice, and their F1 crosses (BCB6 and B6BC, both sensitive to 3MC carcinogenesis) were studied.
- DNA adducts formed in lung DNA were measured by ^{32}P-postlabeling at 1, 2, 4, 7, 14, and 21 days after injection.
- Induction of cytochromes P450 *Cyp1a1* and *Cyp1b1* were measured by quantitative fluorescent real-time PCR.
- Glutathione transferase (GST) α, π, μ, and θ expression levels in fetal lung and liver tissues were measured by Western blotting, while GST activity was measured using 1-chloro-2,4-dinitrobenzene as a substrate.
- 3-MC metabolites formed by *in vitro* metabolism of 3MC by maternal microsomes were analyzed by LC/MS.

Results

- DNA adduct levels were not significantly different between the four strains.
- *Cyp1a1* and *Cyp1b1* were induced by treatment with 3MC, with *Cyp1a1* expression 2-5 times greater in fetal liver than in fetal lung. The only significant strain-specific difference found was a lower level of induction of *Cyp1b1* in B6 mice, particularly in fetal lung, but this probably does not explain the differences between strain susceptibilities.
- All 4 GST isoforms are expressed at low levels in fetal lung and liver in all 4 strains. GST μ was significantly induced by 3MC in BC mice.
- No differences were found in GST activity between strains.
- While some differences in formation of specific metabolites were observed between strains, they could not explain the differences in susceptibility.

Conclusions

- Differences between strains with respect to 3MC carcinogenesis following *in utero* exposure may be due to factors other than metabolism and DNA damage.
- The high inducibility of Phase I enzymes in fetal tissues, coupled with low, uninducible levels of Phase II enzymes probably contributes to the high susceptibility of the fetus to carcinogen-mediated lung tumor induction following *in utero* exposure.

References

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